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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/625,854	07/23/2003	Andre Delacourte	11362.0039.NPUS01	9442

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EXAMINER	
WANG, CHANG YU	
ART UNIT	**PAPER NUMBER**
1649	

DATE MAILED: 02/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/625,854	DELACOURTE ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 12, 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 29-54* is/are pending in the application.

4a) Of the above claim(s) *38 and 44-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26,29-37 and 39-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/10/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/ Election/Restrictions

1. Applicant's election with traverse of Group I and N-terminal truncated/post-translationallv modified β-amyloid variant, A peptide, and species of start position 4, methylation at position 4, Aβ (4-42), and Aβ (5-42) in the reply filed on January 16, 2006 is acknowledged. The traversal is on the ground(s) that the method of screening clearance of β-amyloid in the Group II is complementary to the method of determining the susceptibility to a disease associated with β-amyloid formation/aggregation in the Group I. The potential mechanisms for the Aβ clearance could be through the formation a complex of ApoE or α2-M with Aβ and endocytosis of the Aβ/ApoE or Aβ/a2-M complex by LDL-receptor related protein (LRP), or an immune response of glial cells. In addition, r-secretase, presenilin, and notch have been demonstrated involved in processing APP and generation of Aβ. Therefore, a method for determining whether a person susceptible to a disease associated with Aβ formation/aggregation can be achieved by detecting the genes involved in the process of APP and generation of Aβ at the gene, transcription, translation or posttranslational level with different means, such as proteomics, immunological, RT-PCR or genetic markers approaches. However, Applicant's argument has been fully considered and found persuasive. Therefore, Group II is rejoined to Group I and included in this examination. However, with regard to the traverse of rejoining Group III together with Groups I and II is not found persuasive because the method of determining the susceptibility to a disease

associated with Aβ formation or screening the clearance of Aβ does not necessarily require the product in the Group III. Therefore, Group III is patentably distinct from Groups I and II.

2. The requirement for the rest of the restrictions is still deemed proper and is therefore made FINAL.

3. Claims 26 and 29-54 are pending. Claims 38 and 44-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Group III, there being no allowable generic or linking claim. In addition, claim 37 is also withdrawn from further consideration because of non-elected species. Claims 26, 29-36 and 39-43 are under examination in this office action

Priority

4. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged.

Information Disclosure Statement

5. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

6. Claims 31-36 and 43 are objected to as encompassing non-elected subject matter.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 26, 29-43 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

10. The claims are drawn to a method for determining whether a mammal is susceptible to a disease associated with β-amyloid formation and a method for screening the clearance of Aβ deposition in a mammal comprising comparing the amount of N-terminal truncated/post-translationally modified β-amyloid variant in the said mammal with a control. The specification discloses that there is an increase of N-terminal truncated Aβ peptides in extracts derived from brain tissues of patiens who died of Alzheimer's disease (AD) and animal models by using 2D electrophoresis and detecting immunoblots with anti-N-terminal Aβ antibodies, 6E10 (recognizes residues 4-13 of Aβ) and WO2 (recognizes residues 5-8 of Aβ), and anti-C-terminal Aβ antibodies, 21F12 and ADA40. Applicant also discloses that the increase of N-terminal truncated Aβ can be post-translationally modified by methylation and pyroglutamylation by mass spec analysis. Further, Applicant discloses that the increase of N-terminal truncated Aβ can be detected in the CSF derived from AD patients. However, Applicant fails to teach

how to identify a mammal susceptible to or at risk to develop a disease associated with Aβ formation/aggregation by detecting these modifications. Applicant also fails to teach how to screen the clearance of Aβ or predict the level of Aβ burden using these modifications. The disclosures provided by Applicant have not taught how N-terminal truncated Aβ/post-translationally modified Aβ variant is related to the clearance of Aβ or Aβ burden in a mammal. The prior art has proposed that the clearance of Aβ may be through the mechanisms of receptor-mediated endocytosis of the complex of ApoE or α2-M with Aβ by LDL-receptor related protein (LRP) or receptor for advanced glycation end products (RAGE). The clearance of Aβ may be also through the mechanisms of degradation of Aβ by Zinc metalloendopeptidases, insulin degrading enzyme (IDE or insulysin) or neprilysin (NEP), or may through the immune response of glial cells to generate anti-Aβ antibodies (Tanzi et al. Neuron 2004. 43: 605-608). However, Applicant has not provided any guidance of the correlation between the level of prediction for a disease associated with Aβ formation and the level of detection. The prior art has demonstrated that γ-secretase and presenilin are involved in processing APP and generation of Aβ (Hardy et al. Science 2002. 297: 353-356). Each one of the molecules mentioned above has a potential to affect the clearance or generation of Aβ. Besides, the generation and clearance of Aβ are naturally physiological processes. Therefore, it is difficult to envision what level and what kind of N-terminal truncated Aβ can be considered as abnormal and thus is an Aβ burden for disease or at risk to develop the disease associated with Aβ formation/aggregation. In addition, Applicant

only described some members of the genus of the N-terminal truncated Aβ or post-translationally modified Aβ variants, thus the skilled artisan cannot envision what others species of N-terminal truncated or post-translationally modified Aβ variants to detect. Furthermore, every one of us is at risk of developing a disease associated Aβ formation/aggregation, however, Applicant has not provided any specific information to predict which one of us would develop a disease associated with Aβ formation/aggregation or which one of us would not based on the claimed method. The specification has not taught what would be different in normal people and people at risk for AD in what level of Aβ since the clearance of Aβ occurs naturally in any persons with any conditions. The specification has not taught what level of Aβ is considered as an Aβ burden and what level of Aβ can be considered as free of an Aβ burden. Since the specification has provided no information as to how to predict the level of Aβ burden, screen the clearance of Aβ and to predict what person would develop a disease associated with Aβ formation/aggregation, undue experimentation is required for a person of skill in the art to use the invention.

11. Claims 30 and 39 are further rejected because Applicant fails to disclose how to distinguish the naturally occurring N-terminal truncated Aβ from the exogenous while administering exogenous N-terminal truncated Aβ in a mammal and comparing the amount of N-terminal truncated Aβ from the said mammal with that in a control. Further, Applicant has not provided enough guidance as to whether all N-terminal truncated Aβ

are immunogenic and able to elicit an immune response. Moreover, although it has been disclosed that most AD patients develop anti-Aβ autoantibodies, these anti-Aβ autoantibodies have not been well characterized. It has been speculated that these autoantibodies may help clear Aβ in normal persons (Tanzi et al. Neuron 2004. 43: 605-608). Applicant fails to teach how much increased amount of antibody or reactive T-cells specific for N-terminal truncated Aβ in a mammal can be considered as at risk to develop a disease associated with Aβ-formation/aggregation. Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention. Without such guidance, whether the N-terminal truncated is distinguishable from endogenous Aβ is unpredictable, indicating that undue experimentation is required for those skilled in the art to practice the invention.

12. Thus, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, it would require more undue experimentation to practice the claimed invention.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 26, 29, 31-36, 40-43 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the controls.

Conclusion

NO CLAIM IS ALLOWED.

15. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

16. Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

18. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
January 27, 2006

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER